Acetylsalicylic acid and montelukast block mast cell mediator–related symptoms during rapid desensitization

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Background: Rapid desensitization is a process in which drug-allergic patients receive their target dose in incremental steps, resulting in a state of temporary tolerization. In this manner, first-line therapy can be delivered safely, even in patients who present with severe hypersensitivity reactions (HSRs) to the given agent. A small subset of patients has persistent HSRs during rapid desensitization that can be refractory to antihistamines and corticosteroids.

Objective: To increase the safety and tolerability of rapid desensitization by prostaglandin and leukotriene blockade in patients with refractory mast cell mediator–related symptoms.

Methods: Fourteen adult patients developed HSRs to platinum chemotherapy that persisted during rapid desensitization. All patients had cutaneous symptoms (flushing, pruritus, or urticaria), many with associated systemic reactions. These patients were then pretreated with acetylsalicylic acid, 325 mg orally, and montelukast, 10 mg orally, 2 days before and on the day of desensitization. Response to subsequent desensitizations was assessed by medical record review and was compared with a group of matched historic control patients who received methylprednisolone for HSRs during desensitization.

Results: Seventy-eight desensitizations in 14 patients were performed. Using acetylsalicylic acid and montelukast, 86% of patients (12/14) experienced substantial improvement in symptoms (grade 0.5 vs grade 2.14, $P < .0001$). Reduction in symptoms during desensitization was also significantly greater than that experienced by historic control patients who received methylprednisolone pretreatment (grade 0.5 vs grade 1.75, $P = .0008$). All patients received their target dose of chemotherapy, and there were no severe systemic HSRs.

Conclusions: Pretreatment with acetylsalicylic acid and montelukast lessens the severity of HSRs during rapid desensitization.

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INTRODUCTION

Rapid desensitization for hypersensitivity reactions (HSRs) to medications, including chemotherapy medications, monoclonal antibodies, and antibiotics, has become the standard of care at our institution. Rapid desensitization is a process in which drug-allergic patients receive their target dose in incremental steps, resulting in a state of temporary tolerization. In this manner, first-line therapy can be delivered safely, even in patients who present with HSRs to the given agent.

During the past 5 years, we have reported our experience with rapid desensitizations. Initially, we described 77 desensitizations to paclitaxel and docetaxel and 35 desensitizations to carboplatin, using a standardized 12-step protocol.[1,2] We followed this with a report of 255 desensitizations that occurred in both the inpatient and the outpatient setting, targeted against both chemotherapeutic and monoclonal antibody therapies.[3] Most recently, we reported data from 2005 to 2006 on the outcomes and safety of 413 chemotherapy or monoclonal antibody desensitizations performed on 98 patients at our institution.[4] In this report, our standardized 12-step protocol was used to deliver a wide variety of agents, including carboplatin, cisplatin, oxaliplatin, paclitaxel, liposomal doxorubicin, doxorubicin, and rituximab, both intravenously and intraperitoneally. We found that in 94% of our desensitization cases, reactions were either nonexistent or mild. Furthermore, there were no life-threatening HSRs or deaths, and all patients received their full target dose.

There remains a subset of patients who require high-dose histamine receptor blockade as well as corticosteroid therapy to tolerate their desensitization. Some patients have symptoms during desensitization that persist even after administration of antihistamines and methylprednisolone. We sought to identify a steroid-sparing, adjunctive therapy to ameliorate these refractory symptoms. Because flushing and vasodilatation are mediated by prostaglandins and leukotrienes, we chose to block these mast cell mediators released during HSRs. We added acetylsalicylic acid, 325 mg orally and montelukast, 10 mg orally, as prophylactic medications, and the results of 78 desensitizations performed in 14 patients are reported.

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METHODS

The collaboration between investigators at Dana Farber Cancer Institute and Brigham and Women's Hospital, Allergy and Medical Intensive Care divisions, was approved by the Human Research Committee (IRB Protocol 2008P-000821/1). The medical records of patients who underwent rapid desensitization between January 2007 and May 2008 were reviewed.

The inclusion criteria were (1) age 18 years or older, (2) ability to provide informed consent, and (3) patients who presented with HSRs during rapid desensitization. Patients who presented with flushing and/or severe hypersensitivity symptoms received acetylsalicylic acid, 325 mg orally, and montelukast, 10 mg orally, as prophylactic medication in further desensitizations for 2 days before and on the day of desensitization.

Historic control patients were selected from medical record review of the patient group who underwent rapid desensitization between January 2005 and December 2006. Control patients were chosen if they had an HSR to a platinum chemotherapy involving a diffuse skin reaction and/or systemic symptoms (bronchospasm, angioedema, vomiting, or diarrhea), subsequently underwent 2 to 6 desensitization courses, and had an HSR during desensitization. However, instead of receiving acetylsalicylic acid and montelukast as additional prophylactic medication in future desensitizations, all control patients received methylprednisolone, 0.5 mg/kg intravenously (IV).

Skin Test for Hypersensitivity

Skin tests with carboplatin or oxaliplatin were performed in all patients in the acetylsalicylic acid/montelukast group. For prick testing, carboplatin, 10 mg/mL, and oxaliplatin, 5 mg/mL, were used. For intradermal testing carboplatin (1 and 10 mg/mL) and oxaliplatin (0.5 and 5 mg/mL) were injected.[2,3,5] Skin tests were performed at least 2 weeks after the initial reaction to avoid false-negative results; a positive reaction was defined as a wheal of 3 mm greater than that of a negative control (diluent), and histamine (10 mg/mL) was used as a positive control.

Rapid Desensitization

Initial desensitizations occurred in the medical intensive care unit, with 1-to-1 nursing using the 12-step rapid desensitization protocol as indicated in Table l for oxaliplatin.[2,3] Subsequent desensitizations were performed in a Dana Farber Cancer Institute outpatient infusion center; the interval between chemotherapy treatments was 3 to 4 weeks, as dictated by standard oncology protocols. All patients were pretreated with diphenhydramine, 25 mg IV, and ranitidine, 50 mg IV, 20 minutes before the infusion. One patient in the acetylsalicylic acid/montelukast group had an initial life-threatening HSR and was given a 16-step protocol (bag 1 diluted 1:1,000).

Management of HSRs During Desensitization

Hypersensitivity reactions were classified as absent (0) if there was no reaction, mild (1) if only a limited extent of the skin (<50%) was involved (flushing, hives, or pruritus), moderate (2) if there was generalized involvement of the skin or angioedema (excluding laryngeal angioedema), and severe (3) if there was laryngeal angioedema or when respiratory, gastrointestinal, or cardiovascular symptoms were associated with cutaneous symptoms (based on Ring classification).[6]

Reactions that occurred during the desensitization were treated by pausing the infusion. For grades 1 and 2 HSRs, additional H_1-blockers (diphenhydramine, 50 mg IV, or hydroxyzine, 50 mg orally) were given. For grade 3 reactions, additional H_2-blockers (either famotidine, 20 mg IV, or ranitidine, 50 mg IV) and methylprednisolone, 0.5 mg/kg IV, were administered. Oxygen and nebulized albuterol were

Table 1. Standard 12-Step Chemotherapy Desensitization Protocol for Oxaliplatin[a]

Step	Solution	Rate, mL/h	Time, min	Volume infused per step, mL	Dose administered with this step, mg	Cumulative dose, mg
1	1	2.0	15	0.50	0.0026	0.0026
2	1	5.0	15	1.25	0.0066	0.0092
3	1	10.0	15	2.50	0.0132	0.0224
4	1	20.0	15	5.00	0.0264	0.0488
5	2	5.0	15	1.25	0.0660	0.1148
6	2	10.0	15	2.50	0.1320	0.2468
7	2	20.0	15	5.00	0.2640	0.5108
8	2	40.0	15	10.00	0.5280	1.0388
9	3	10.0	15	2.50	1.3096	2.3485
10	3	20.0	15	5.00	2.6192	4.9677
11	3	40.0	15	10.00	5.2384	10.2061
12	3	80.0	174.37	232.50	121.7939	132.0000

[a] The target dose was 132 mg (standard volume per bag, 250 mL; final rate of infusion, 80 mL/h). Solution 1 contained 0.005 mg/mL (total per bag, 132 mg). Solution 2 contained 0.053 mg/mL (total per bag, 13.20 mg). Solution 3 contained 0.524 mg/mL (total per bag, 130.96 mg). Diphenhydramine, 25 mg intravenously, × 1 and ranitidine, 50 mg intravenously, × 1 were given 20 minutes before the infusion. In addition, acetylsalicylic acid, 325 mg orally daily, and montelukast, 10 mg orally daily, were taken for 2 days before and were given 60 minutes before the desensitization protocol was initiated. The total time was 339.375 minutes. The total volume infused per step was 5.66 mL.

used whenever respiratory symptoms were present. Epinephrine, 0.3 mL (1 mg/mL), was available in the event of hypotension and/or throat swelling but was never required. Once the reaction subsided, the protocol was restarted from the step at which it had been paused.

Statistical Analysis

A paired *t* test was performed to analyze the response of the study group before and after acetylsalicylic acid/montelukast pretreatment and to analyze the response of the historic control group before and after methylprednisolone pretreatment. An independent *t* test was used to compare the study group response to acetylsalicylic acid/montelukast pretreatment with the control group response to methylprednisolone pretreatment. $P < .05$ were considered statistically significant.

RESULTS

After medical record review, 14 patients met inclusion criteria for the acetylsalicylic acid/montelukast group (Table 2). All patients were female. The mean age was 61 years (equal median, 61 years), with a minimum of 47 years and a maximum of 75 years. Eighty-six percent of the patients (12/14) were treated with carboplatin for ovarian or peritoneal cancer. Two patients were treated with oxaliplatin for colon cancer. Except for patient 5, all patients were treated for recurrent malignancy. Patient 14 was previously enrolled in our desensitization program; all other patients had to suspend their chemotherapy because of an HSR and were not desensitized previously.

The first reaction before desensitization was grade 2 or 3 for all patients (Table 2). All 14 patients had positive skin test results (Table 2; 25% in SPT and 75% in ID for carboplatin and 100% in ID for oxaliplatin). The total number of desensitization treatments ranged from 2 to 10 (mean, 5.5), with a total of 78 (some patients are still enrolled in the desensitization program; Table 3). Reactions occurred during the first desensitization in many of the patients (8/14, 57%); 21.5% occurred during the second desensitization (3/14) and the remaining 21.5% (3/14) after 3 or more desensitizations. Cutaneous symptoms were the main clinical presentation (present in 100% of the patients). Some patients had additional symptoms, including bronchospasm, angioedema, vomiting, or diarrhea. Fifty percent of the patients (7/14) had grade 3 reactions, 14% (2/14) had grade 2, and 36% (5/14) had grade 1 reactions. No patient needed intramuscular epinephrine, and all patients received their full target dose.

In 7 patients, acetylsalicylic acid and montelukast were added to the standard premedication regimen in the desensitization after the first reaction; they were given for 2 days before and on the day of the desensitization. In 4 patients, acetylsalicylic acid and montelukast were added 2 to 3 desensitizations later. In 4 patients, methylprednisolone was added to the standard prophylactic premedication without any improvement; then, acetylsalicylic acid and montelukast were added with substantial benefit. Under the acetylsalicylic acid and montelukast protocol, 12 of 14 patients (86%) were able to tolerate further desensitizations with a less severe HSR (5 patients) or no reaction (7 patients) (Fig 1). The average reaction grade before acetylsalicylic acid/montelukast pretreatment was 2.14, whereas after acetylsalicylic acid/montelukast pretreatment the average reaction grade was 0.5 ($P < .001$). Patient 12 had significant improvement in the first 3 desensitizations after addition of acetylsalicylic acid and montelukast and then had a grade 3 reaction during desensitization 8. Desensitizations 9 to 12 occurred without major incident. Patients 6 and 13 did not experience any improvement after the introduction of acetylsalicylic acid and montelukast, but both of these patients had grade 1 reactions during desensitization.

Eight patients from the 2005 to 2006 patient cohort served as appropriately matched historic control patients for the

Table 2. Patient Characteristics

Patient No.	Age, y	Type of cancer	Primary/recurrent cancer	Chemotherapeutic agent inducing HSRs	Course at which initial HSR occurred	Severity of the initial HSR	Positive skin test results
1	68	Ovarian	Recurrent	Carboplatin	8	3	SPT (10 mg/mL)
2	47	Ovarian	Recurrent	Carboplatin	8	3	ID (10 mg/mL)
3	60	Ovarian	Recurrent	Carboplatin	8	3	ID (1 mg/mL)
4	51	Ovarian	Recurrent	Carboplatin	7	3	ID (10 mg/mL)
5	66	Peritoneal	Primary	Carboplatin	7	3	SPT (10 mg/mL)
6	54	Ovarian	Recurrent	Carboplatin	6	2	ID (1 mg/mL)
7	63	Ovarian	Recurrent	Carboplatin	9	3	ID (10 mg/mL)
8	62	Ovarian	Recurrent	Carboplatin	11	3	SPT (10 mg/mL)
9	61	Peritoneal	Recurrent	Carboplatin	7	2	ID (0.1 mg/mL)
10	59	Ovarian	Recurrent	Carboplatin	5	2	ID (1 mg/mL)
11	75	Colon	Recurrent	Oxaliplatin	Unknown	3	ID (0.5 mg/mL)
12	52	Colon	Recurrent	Oxaliplatin	8	3	ID (0.5 mg/mL)
13	60	Ovarian	Recurrent	Carboplatin	13	3	ID (1 mg/mL)
14	72	Ovarian	Recurrent	Carboplatin	15	3	ID (1 mg/mL)

Abbreviations: HSRs, hypersensitivity reactions; ID, intradermal test; SPT, skin prick test.

Table 3. Hypersensitivity Reactions During Desensitization Before and After the Introduction of Acetylsalicylic Acid and Montelukast

Patient No.	No. of desensitization courses	Desensitization No. at which each patient reacted	Desensitization No. at which acetylsalicylic acid and montelukast were added	Severity of the first reaction during desensitization	Reactions after acetylsalicylic acid and montelukast	Additional prophylactic medication
1	2[a]	1	2	3	1	
2	6	3	4	3	1	Methylprednisolone at desensitization 3
3	6	2	5	3	0	
4	6	2	4	1	0	
5	7[a]	1	5	3	0	Methylprednisolone at desensitization 3, 4, 5
6	3[a]	1	2	1	1	
7	6	2	3	1	0	
8	6	3	5	3	0	
9	4	1	2	3	1	
10	6	1	5	2	1	Methylprednisolone at desensitization 2, 3, 4
11	2[a]	1	2	1	0	
12	12[a]	1	4	3	1[b]	Methylprednisolone at desensitization 2, 3, 4, 8
13	2[a]	1	2	1	1	
14	10[a]	7	10	2	0	

[a] Patients still enrolled in desensitization program.
[b] Patient had a grade 0 or 1 reaction in subsequent desensitizations after addition of acetylsalicylic acid and montelukast except desensitization 8, during which she had a grade 3 reaction.

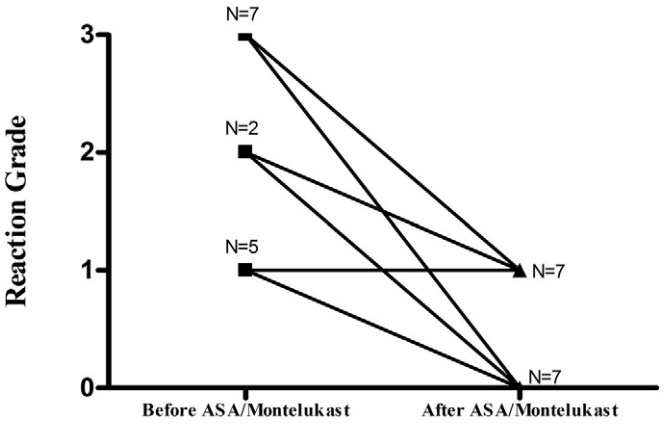

Figure 1. Evolution of severity of reactions before and after acetylsalicylic acid (ASA)/montelukast pretreatment. Under the ASA and montelukast protocol, 86% of patients were able to tolerate further desensitizations, with a less severe hypersensitivity reaction or no reaction (grade 2.14 vs grade 0.5, $P < .001$).

acetylsalicylic acid/montelukast group. Because 1 of the goals of acetylsalicylic acid/montelukast pretreatment was to identify a steroid-sparing adjunctive therapy to ameliorate refractory HSRs during rapid desensitization, a direct comparison with corticosteroid pretreatment was desirable. Therefore, matched patients were chosen for the control group only if they received methylprednisolone as additional prophylactic premedication before rapid desensitization (Table 4). For these patients, the first reaction before desensitization was also grade 2 or 3. The total number of desensitization treatments per patient ranged from 2 to 6 (mean of 4.25), with a total of 34 desensitizations. Reactions occurred during the first desensitization for all control patients. Cutaneous symptoms were also present in all control patients. Thirty-seven percent of the patients (3/8) had grade 3 reactions, 63% (5/8) had grade 2 reactions, and no patient had a grade 1 reaction. As in the acetylsalicylic acid/montelukast group, no patient needed intramuscular epinephrine and all patients received their full target dose.

Methylprednisolone, 0.5 mg/kg IV, was added to the standard premedication regimen in the desensitization after the first reaction for all control patients. With methylprednisolone pretreatment, 5 of 8 patients (62%) were able to tolerate further desensitizations with a less severe HSR (4 patients) or no reaction (1 patient). However, 5 of the 8 control patients still had grade 2 or 3 HSRs during desensitization after methylprednisolone pretreatment, and 2 of the patients who started out with grade 2 HSRs during desensitization then went on to have grade 3 HSRs. Only 1 of the 8 control patients had no reaction when pretreated with methylprednisolone. For the control patients, severity of the first reaction during desensitization was compared with severity of reactions after methylprednisolone and was not significantly different ($P = .20$). Response to acetylsalicylic acid/montelukast pretreatment was compared with response to methylprednisolone pretreatment using an independent t test (Fig 2).

Table 4. Historic Control Patients

Patient No.	Age, y	Type of cancer	Chemotherapeutic agent inducing HSRs	Severity of the initial HSR	No. of desensitization courses	Severity of the first reaction during desensitization	Reactions after methylprednisolone	Additional prophylactic medications/protocol modifications
1	62	Ovarian	Carboplatin	3	2	2	3	Diphenhydramine; step added to protocol
2	30	Ovarian	Carboplatin	3	4	2	0	Diphenhydramine
3	71	Ovarian	Carboplatin	3	3	3	2	Diphenhydramine, metoclopramide
4	68	Ovarian	Carboplatin	3	5	3	3	Diphenhydramine; step added to protocol
5	52	Ovarian	Carboplatin	3	5	3	2	Diphenhydramine
6	41	Cervical	Cisplatin	3	5	2	3	Diphenhydramine; step added to protocol
7	64	Ovarian	Carboplatin	3	4	2	1	none
8	73	Ovarian	Carboplatin	2	6	2	1	Diphenhydramine; step added to protocol

Abbreviation: HSRs, hypersensitivity reactions.

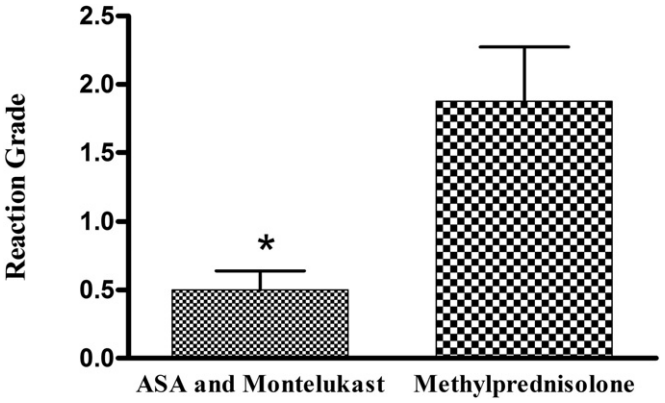

Figure 2. Comparison of the effects of acetylsalicylic acid (ASA)/montelukast vs methylprednisolone pretreatment. ASA/montelukast pretreatment was more effective at blocking hypersensitivity reactions during rapid desensitization than was methylprednisolone (*$P < .001$; mean [SEM], 0.5000 [0.1387], n = 14, vs 1.875 [0.3981], n = 8).

The average reaction grade after methylprednisolone pretreatment was 1.75, whereas the average reaction grade in the acetylsalicylic acid/montelukast group was 0.5 ($P < .001$).

DISCUSSION

Rapid desensitization has allowed oncology patients to be treated with first-line therapy, as shown previously.[1–4] In our institution, we have performed more than 800 chemotherapy desensitizations in which no cardiopulmonary arrests or deaths have occurred. Only 1 desensitization-related HSR has required epinephrine administration in the past 7 years. To further improve the safety of this procedure, we hypothesized that pretreatment with acetylsalicylic acid and montelukast before drug desensitization could block refractory mast cell–mediated symptoms that occurred during desensitization.

A population of 14 patients who presented with skin reactions, including pruritus, flushing, and/or urticaria during their initial desensitization protocol despite antihistamine premedication, was selected. Nine patients (64%) had generalized skin reactions that were associated with other systemic symptoms, and 5 patients had bronchospasm (36%). Of the 5 patients who presented with a limited skin reaction, the reaction was completely blocked by pretreatment with acetylsalicylic acid and montelukast in 3 patients (60%); the other 2 patients continued to have skin symptoms during subsequent desensitizations. Two patients presented with more extensive skin reactions with nonlaryngeal angioedema during their initial desensitization. Both of these patients responded to pretreatment with acetylsalicylic acid and montelukast, which either blocked the reaction completely or reduced it to a much milder reaction confined to the skin alone without any associated angioedema.

All patients who presented with generalized skin reactions and systemic symptoms had substantial benefit from acetylsalicylic acid and montelukast pretreatment; 3 of these patients had no reaction, 3 patients had flushing, and 1 patient had residual pruritus and rash. Four of the 5 patients with respiratory symptoms before acetylsalicylic acid and montelukast pretreatment did not experience dyspnea, chest tightness, or wheeze once this treatment was added. Interestingly, methylprednisolone had been added to the standard premedication regimen for 4 of the patients during prior desensitizations and had failed to result in amelioration of the reaction. After acetylsalicylic acid and montelukast pretreatment, 3 of the 4 patients (75%) had either mild or no reaction during subsequent desensitizations. This corresponds with the observation that most of the historic control patients, who all received methylprednisolone pretreatment, still had grade 2 or 3 HSRs during desensitization, suggesting a different target cell or mechanism of inhibition between the 2 pretreatment protocols.

Patient 12 from the acetylsalicylic acid/montelukast group, 1 of the patients who initially presented with both a generalized skin reaction and systemic symptoms (grade 3), also had substantial benefit from acetylsalicylic acid and montelukast pre-

treatment, despite a grade 3 reaction during desensitization 8. Three of her 4 desensitizations before acetylsalicylic acid and montelukast pretreatment were characterized by generalized skin reaction, bronchospasm, and throat tightness. Acetylsalicylic acid and montelukast pretreatment was introduced at desensitization 5, and she tolerated all subsequent desensitizations except desensitization 8 with either no reaction or with a mild skin reaction only. During desensitization 8, however, she had a generalized rash, dyspnea, and a transient oxygen desaturation that improved after the infusion was paused and methylprednisolone was administered. Her protocol was not altered for subsequent desensitizations because the previous 3 desensitizations were well tolerated. Further desensitizations were also well tolerated. We are unable to explain her reaction during desensitization 8, but her course with acetylsalicylic acid and montelukast pretreatment resulted in grade 0 or 1 reactions in 7 of 8 subsequent desensitizations. As this patient's experience shows, acetylsalicylic acid and montelukast pretreatment can provide benefit to patients yet may fail to block all breakthrough reactions for reasons that are not currently understood.

In IgE-mediated anaphylaxis, activated mast cells release histamine, tryptase, chymase, and proteoglycans from their intracellular granules. Subsequently, prostaglandins and leukotrienes are synthesized from membrane arachidonic acid. The combination of these mediators leads to the symptoms that characterize anaphylaxis. Acetylsalicylic acid has been used to block niacin-induced flushing, which is thought to be mediated by prostaglandin D2 (PGD2); indeed, a recent study showed acetylsalicylic acid, 650 mg orally, before administration of niacin significantly reduced the incidence, duration, and severity of niacin-induced flushing.[7] Overproduction of PGD2 also contributes to many of the symptoms of mastocytosis, as illustrated by the markedly increased excretion of the major urinary metabolite of PGD2, PGD2-M, in the urine of patients with indolent systemic mastocytosis.[8] Because of this, in our institution we have successfully used high-dose oral acetylsalicylic acid to block flushing in patients with indolent systemic mastocytosis.

Products of the 5-lipoxygenase pathway, namely leukotrienes (LT) C4, D4, and E4, are known to induce cutaneous vasodilatation, resulting in erythema and wheal formation when experimentally injected into human skin.[9] Furthermore, when LTB4 is injected with PGD2, the resulting wheal and flare are markedly exaggerated and characterized histologically by edema and a neutrophilic infiltrate. Perhaps because of this, antileukotriene therapies have been used anecdotally as adjunctive treatment for chronic urticaria associated with food or drug ingestion, primary cold urticaria, delayed-pressure urticaria, and dermatographism.[10] Their use in treatment of bronchospasm is well known and widely used.

Pretreatment with acetylsalicylic acid and montelukast resulted in substantial improvement in symptoms in 12 of 14 patients (86%) described here, with the greatest benefit seen for patients with more severe reactions during initial rapid desensitization. The effect of acetylsalicylic acid and montelukast pretreatment in the study group was significantly superior to that of methylprednisolone pretreatment in a group of historic control patients. Cutaneous and respiratory symptoms were predominantly affected. Given the known role for prostaglandins and leukotrienes in flushing, urticaria, and bronchospasm, this probably can be attributed to blockade of these mediators. Further studies examining the effect of acetylsalicylic acid and montelukast treatment on such parameters as urinary leukotrienes and prostaglandin metabolites are ongoing at our institution, which may also help elucidate which patient populations will benefit most. Therefore, blockade of prostaglandins and leukotrienes may be a useful and steroid-sparing adjunctive therapy to increase success rates for rapid desensitizations.

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